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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/666,870	09/20/2000	Andrew D. Ellington	119927-1030	8382

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EXAMINER	
EPPERSON, JON D	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 04/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/666,870	ELLINGTON ET AL.	
	Examiner	Art Unit	
	Jon D. Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *47-49,54-57,59-64 and 66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47-49,54-57,59-64 and 66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *10/27/04 Affidavits*.

DETAILED ACTION

Status of the Application

1. The Response filed October 27, 2004 is acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

3. Claims 47-49 and 54-66 were pending. Applicants canceled claims 58 and 65 (e.g., see 10/27/04 Response, page 5, paragraph 1). In addition, Applicants amended claims 49, 54, 61 and 62. Thus, claims 47-49, 54-57, 59-64 and 66 are currently pending and examined on the merits.

Withdrawn Objections/Rejections

4. The Breaker et al. rejection under 35 U.S.C. § 102(a) is withdrawn in part (see below) as a result of Applicants' arguments and/or amendments. All other rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Oath/Declaration

5. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application-by-application number and filing date is required. See MPEP §§ 602.01 and 602.02.

In view of the Affidavits (131 or 132) submitted on February 11, 2004 (see especially page 1, paragraph 1), it is clear that the oath or declaration is defective because Kristin Thompson (formerly Kristin Marshall) is not listed as a co-inventor i.e., the full name of all inventors is not provided.

Response

6. Applicant argue, "... a Supplemental Declaration to the February 11, 2004 Declaration of Prior Invention under 37 C.F.R. § 1.131, as well as a new Affidavit in compliance with 37 C.F.R. § 1.131 are being submitted herewith" (e.g., see 10/27/04 Response, page 10, section V).

This is not found persuasive for the following reasons:

The Examiner contends the supplemental Declaration/Affidavit does not address the issue. Drs. Andrew Ellington, Kristin Thompson and Michael Robertson stated under penalty of perjury that Kristin Thompson was an inventor of the currently claimed invention (e.g., see 2/11/04 Declaration of Prior Invention under 37 C.F. R. § 1.131, "We, Andrew Ellington, Kristin Thompson and Michael Robertson, invented the inventions claimed in the case" (emphasis added); see also signature dated 2/9/04 by Kristin Thompson on page 6). Thus, the oath is defective because Kristin Thompson (formerly Kristin Marshall) is not listed as co-inventor in accordance with MPEP §§ 602.01 and 602.02. Simply removing the name of Kristin Thompson in the current supplemental Declaration/Affidavit does not negate in any way the declaration previously made by Drs. Andrew Ellington, Kristin Thompson and Michael Robertson, which is now of record in this case.

Claims Rejections - 35 U.S.C. 102

7. Claims 47, 49, 54-57, 59 and 61-64 and 66 are rejected under 35 U.S.C. 102(a) as being anticipated by Marshall et al (Marshall, K. A.; Ellington, A. D. "Training ribozymes to switch" Nature Structural Biology **November 1999**, 6 (11), 992-4).

For ***claims 47, 59 and 66***, Marshall et al discloses "aptazyme chips" wherein different ribozyme ligases are immobilized on beads in wells to monitor the presence and concentrations of different metabolites or proteins (see Marshall et al, entire document, especially figure 3; see also page 994, last paragraph), which anticipates claims 47, 59 and 66. For example, Marshall et al discloses aptazyme chips for "monitor[ing] the presence and concentrations of different metabolites or proteins" wherein a "ribozyme ligase", which anticipates the preamble of claim 47 because an "aptazyme reaction" is being "detected" when the ribozyme ligase covalently bonds to a reporter in the presence of cognate effectors. Marshall et al also discloses "aptazymes" on a solid support, which reads on lines 2-5 of claim 47 (see Marshall et al, figure 3, "ribozyme ligases ... are shown immobilized on beads in wells ... [o]ne advantage of this scheme is that covalent immobilization of reporters ... should allow extremely stringent wash steps to be employed"). Marshall et al also discloses "at least one analyte" and "providing substrate tagged to be detectable" in lines 7-8 of claim 47 (see Marshall et al, figure 3, "ribozyme ligases ... immobilized on beads in wells and mixtures of analytes and fluorescently tagged substrates have been added to each well"). Marshall et al also discloses the immobilization of a substrate to the aptazyme upon activation of the aptazyme with an analyte wherein a signal is produced after washing unbound substrate off the substrate

(see Marshall et al, figure 3, "after reaction and washing, the presence and amounts of co-immobilized fluorescent tags are indicative of he amounts of ligands that were present during the reaction"). Please also note that Marshall et al discloses applicants preferred embodiment (compare Marshall et al, figure 3 and page 994, last paragraph to applicant's specification, pages 60-61, especially page 60, line 19 which references the Marshall et al paper).

For **claims 49 and 61**, Marshall et al discloses the use of "amplification" for increasing the amount of aptamer or aptazyme with the desired characteristics and thus increase the signal produced (see Marshall et al, figure 1) (see also Marshall, page 994 last paragraph, "Interestingly, aptazyme ligases have the unique property of being able to transduce effectors into templates that can be amplified, affording an additional boost in signal prior to detection"), which anticipates claim 49.

For ***claims 54 and 62***, Marshall et al discloses fluorescently tagged substrates (see Marshall et al, page 993, figure 3).

For ***claims 55-56 and 63-64***, Marshall et al discloses beads in wells on a multiwell plate (see Marshall et al, page 993, figure 3).

For ***claim 57***, Marshall et al discloses different aptazymes immobilized in different wells (see Marshall et al, page 993, figure 3).

8. Claims 47, 49, 54, 61-62 and 66 are rejected under 35 U.S.C. 102(a) as being anticipated by Hesselberth et al (Hesselberth, J.; Robertson, M. P.; Jhaveri, S.; Ellington, A. D. "In vitro

selection of nucleic acids for diagnostic applications" Reviews in Molecular *Biotechnology* **March 2000**, *74*, 15-25).

For ***claims 47, 59 and 66***, Hesselberth et al discloses methods for the "high-throughput construction of chips to sense proteomes and metabolomes" (see Hesselberth et al, entire document, pages 23-24; section 5), which anticipates claims 47, 59 and 66. For example, Hesselberth et al discloses that "aptazymes" can be "covalently immobilize[d] ... in discrete sectors of arrays" like "chip[s]" (see Hesselberth et al, page 24, last paragraph, "For example, a host of signaling aptamers could be synthesized with terminal amines, immobilized on glass, and an analyte mixture could be applied to the glass surface"). Hesselberth et al also discloses method steps for using the immobilized aptazymes to detect individual analytes by their ability to "pull down" labeled substrates that can then be detected after washing away unbound substrate (see Hesselberth et al, page 24, last paragraph, "The presence of quantities of individual analytes could then be determined by monitoring the changes in fluorescence intensity in individual sectors of the chip. Similarly, aptazymes could be immobilized and analytes and oligonucleotide tags introduced together. Since the pairing between the aptazymes and the oligonucleotide tags can be altered at will, analytes could activate specific aptamers in specific sectors to pull down specific tags. In this way, analyte detection might not only be spatially but also spectrally resolved. Moreover because the tags are covalently immobilized to the aptazyme, which in turn covalently immobilized to the chip surface, aptazyme chips can be stringently washed to reduce non-specific binding and background").

For ***claims 49 and 61***, Hesselberth et al discloses the ribozymes with appended tags can be "preferentially amplified" (see Hesselberth et al, entire document, especially page 16, paragraph 1), which anticipates claim 49.

For ***claims 54 and 62***, Hesselberth et al discloses fluorescent substrates (see Hesselberth et al, page 24, column 1, last paragraph).

Response

9. Applicant's arguments directed to the above 35 U.S.C. § 102 rejection(s) were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicants argue, "... new Affidavit by the named inventors of the instant application, Dr. Andrew D. Ellington, and Dr. Michael Robertson, Dr. J. Colin Cox, Dr. Timothy E. Reidel, and Dr. Eric A. Davidson, under 37 C.F.R. § 1.131 ('the new Affidavit'). The Affidavit demonstrates that the Marshall reference is unavailable as prior art in the instant application. The Marshall reference describes the work of Dr. Ellington, a named inventor in the instant application, as well as a named author of the Marshall reference. The Marshall publication refers to work that ultimately generated the aptamer constructs, arrays, and methods of the claimed invention. In light of the fact that the Marshall reference represents the scientific publication of this work, the methods recited by pending claims ... were necessarily invented before the publication date of the Marshall reference" (e.g., see 10/27/04 Response, pages 5-7; see also Hesselberth section where similar arguments were made).

This is not found persuasive for the following reasons:

The Examiner contends that the Declaration/Affidavit is defective because **[1]** although it is not clear whether Applicants are trying to antedate the reference under 37 C.F. R. § 1.131 or show attribution under 37 C.F.R. § 1.132, to the extent that Applicants are trying to antedate the reference the Examiner contends that no evidentiary support for this position has been provided. With respect to filing declarations under 37 CFR § 1.131, the showing of facts shall be such, in character and weight, as to establish reduction to practice prior or the effective date of the reference, or conception of the invention prior to the effective date of the reference coupled with due diligence from said date to a subsequent reduction to practice or to the filing of the application. Original exhibits or drawings or records or photocopies thereof ***must accompany and form part of the affidavit or declaration*** or their absence satisfactorily explained. See MPEP §715.07. Furthermore, the Declaration/Affidavit is defective because **[2]** it does not include the name of one of the inventors i.e., Kristin Thompson (e.g., see 2/11/04 Declaration of Prior Invention under 37 C.F. R. § 1.131, "We, Andrew Ellington, Kristin Thompson and Michael Robertson, invented the inventions claimed in the case" (emphasis added); see also signature dated 2/9/04 by Kristin Thompson on page 6) and thus cannot be used to antedate the reference because there is no statement explaining that less than all of the inventors contributed to the claimed invention (e.g., see MPEP § 715.04). Finally, to the extent that Applicants are trying to show attribution (e.g., Katz declaration) the new supplemental Declaration/Affidavit is also defective because **[3]** there is evidence that it does not represent Applicants' own work (e.g., see MPEP § 716.10, "An uncontradicted 'unequivocal statement' from the applicant regarding the subject matter disclosed in an article, patent, or published application will be accepted as

establishing inventorship. In re DeBaun, 687 F.2d 459, 463, 214 USPQ 933, 936 (CCPA 1982). However, a statement by the applicants regarding their inventorship in view of an article, patent, or published application ***may not be sufficient where there is evidence to the contrary***. Ex parte Kroger, 218 USPQ 370 (Bd. App. 1982) (a rejection under 35 U.S.C. 102(f) was affirmed notwithstanding declarations by the alleged actual inventors as to their inventorship in view of a nonapplicant author submitting a letter declaring the author's inventorship); In re Carreira, 532 F.2d 1356, 189 USPQ 461 (CCPA 1976) (disclaiming declarations from patentees were directed at the generic invention and not at the claimed species, hence no need to consider derivation of the subject matter)"). In the present case, as in Ex parte Kroger, a nonapplicant [Kristin Thompson, formerly Kristin Marshall] has submitted a letter declaring the author's inventorship (e.g., see 2/11/04 Declaration of Prior Invention under 37 C.F. R. § 1.131, "We, Andrew Ellington, Kristin Thompson [formerly Kristin Marshall] and Michael Robertson, invented the inventions claimed in the case" (emphasis added); see also signature dated 2/9/04 by Kristin Thompson on page 6). Thus, sufficient evidence has been set forth consistent with *Ex parte Krogre*. Furthermore, if Applicants intend a declaration of attribution then Applicants should file said declaration under 37 C.F.R. § 1.132 to make their intentions clear.

Accordingly, the 35 U.S.C. § 102 rejection(s) cited above are hereby maintained.

10. Claims 47-48, 54, 59-60, 62-63 and 66 are rejected under 35 U.S.C. 102(a) as being anticipated by Breaker et al. (WO 00/26226) (Date of Patent is **May 11, 2000**).

For ***claims 47, 59 and 66***, Breaker et al. (see entire document) disclose methods for making and using "aptazyme chips", which anticipates claims 47 and 59. For

example, Breaker et al. disclose providing a solid support having a heterogeneous mixture of aptazyme constructs covalently immobilized thereon (e.g., see figure 17 wherein aptazyme constructs cGMP, ATP, FMN, theo and cAMP are shown immobilized on positions A1, A2, A3, A4 and B1, respectively; see also column 4, lines 17; see especially page 21, line 21). Breaker et al. also disclose at least one analyte (e.g., see figure 16 wherein the DNA is exposed to a sample of interest e.g., ATP). Breaker et al. also disclose providing a nucleic acid substrate tagged to be detectable exposing the nucleic acid substrate and at least one analyte to the immobilized aptazymes, whereby activation of the aptazyme reaction by the analyte produces a signal when the nucleic acid substrate is bound to the immobilized aptazymes, washing unbound substrate off the solid support and detecting the signal from the bound nucleic acid substrate (e.g., see black spots in figure 16; see also page 17, lines 10-19; see also Examples).

For ***claim 48 and 60***, Breaker et al. disclose automation (e.g., see page 21, line 19 wherein "automation" is disclosed; see also figure 16 wherein a microchip is disclosed). The use of a microchip would inherently involve automation because microchips were designed for this purpose.

For ***claims 54 and 62***, Breaker et al. disclose, for example, enzyme tags (e.g., see page 17, line 14 wherein "self cleavage" is disclosed).

For ***claims 55 and 63***, Breaker et al. disclose a multiwell plate (e.g., see page 36, line 29 wherein a microtiter plate is disclose; see also figure 16).

Response

11. Applicant's arguments directed to the above 35 U.S.C. § 102 rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "Breaker I does not disclose how to automate a method for detecting an aptazyme reaction using immobilized aptazyme constructs, as provided by claims 47, 59 and 66 of the instant invention" (10/27/04 Response, page 10, last paragraph).

[2] Applicants argue, "automation in Breaker I (page 21, line 19) noted by the Examiner teaches an automated method to identify DNA molecules, not an automated method for detecting aptazyme reactions, as provided by claims 48 and 60 of the instant invention (e.g., 10/27/04 Response, page 11, paragraph 1).

[3] Applicants argue, "Likewise, the microtiter plate in Breaker I noted by the Examiner (page 36, line 29) teaches the use of a microtiter plate during an in vitro selection process, not for use in detecting an aptazyme reaction" (e.g., see 10/27/04 Response, page 11, paragraph 1).

[4] Applicants argue, "the reference to signal amplification by PCR cited by the Examiner ... teaches signal amplification during an vitro selection process ... To avoid vagueness in the claim language, Applicants have amended claims 49 and 71 to reflect the signal is "PCR amplified for detection" (e.g., see 10/27/04 Response, page 11, paragraph 1).

[5] Applicant argue that they have amended claims 54 and 62 to exclude fluorescently tagged nucleic acid substrates (e.g., see 10/27/04 Response, page 11, second paragraph).

This is not found persuasive for the following reasons:

[1] The Examiner contends that claims 47, 59 and 66 are not drawn to an "automated" process as was mistakenly purported and, as a result, Applicants' arguments are moot.

[2] The Examiner respectfully disagrees. Applicants' arguments are not commensurate in scope with the claims because claims 48 and 60 do not state which of the method steps need to be automated (e.g., see claim 48, "The method of claim 47, wherein the method is automated"). Thus, any of the method steps could be automated including "providing a solid support having a heterogeneous mixture of aptazyme constructs" (e.g., see claim 47). Consequently, an automated steps for selecting the aptazymes that are subsequently used to create the solid support falls within the scope of an automated method for "providing ... a heterogeneous mixture of aptazyme constructs"). In addition, automation would be immediately envisioned from the use of a microchip (e.g., see figure 16), which was designed for automation.

[3] The Examiner respectfully disagrees. Applicants' arguments are not commensurate in scope with the claims because claims 55 and 63 only state (by reference to the independent claims) that the method must "provid[e] a solid support having a heterogeneous mixture of aptazyme construct covalently immobilized thereon" (e.g., see claim 47) and, as a result, does not require that any "detecting" step take place. In addition, the use of the microtiter plate falls within the "Allosteric Ribozyme characterization" section and thus would be more broadly applied to the characterization of the allosteric ribozymes on the chip (i.e., the use of the microtiter plate does not seem to be limited to the in vitro selection process alone).

[4] The Examiner finds these arguments and/or amendments persuasive and the rejection is hereby withdrawn in part with respect to claims 49 and 61.

[5] The Examiner contends that nucleic acid substrates are tagged with an enzyme via "self-cleavage" (e.g., see newly amended rejection above).

Accordingly, the 35 U.S.C. § 102 rejection cited above is hereby maintained.

12. Claims 66 is rejected under 35 U.S.C. 102(b) as being anticipated by Asher et al. (WO 98/08974) (Date of Publication is March 5, 1998).

For ***claim 66***, Asher et al. disclose (see entire document) catalytic nucleic acids and their diagnostic use (see Asher et al, abstract), which anticipates claim 66. For example, Asher et al. disclose providing an array having one or more aptazyme constructs disposed thereon at discrete locations by immobilization of said aptazyme constructs on a solid support (e.g., see figure 1 step 3 showing the immobilization processes using streptavidin/avidin as the linker; see also page 4, lines 18-22, "The biotin, is then allowed to react with avidin which is present on a solid support, such as Stepravidin beads (SA), so that each molecule of the random array becomes immobilized onto a solid support"). Please note that the aptazyme constructs in this scenario comprise a random sequence (R) that cleave the substrate (S) in "cis" (e.g., see page 24, Example 1, lines 9-15; see also figure 1, step 1, see also figure 1, step 4(b)(i) and 4(b)(ii); see also page 14, lines 21-29). In addition, Asher et al. disclose contacting said aptazyme constructs with a substrate tagged with a detectable label (e.g., see figure 1, step 1 wherein the substrate is represented by the "S" i.e., the aptazyme is cis-acting; see also figure 1, step 6 wherein a PCR amplified tag is shown; see also page 16, last paragraph;

see also page 8, lines 10-15, "For example, the catalytic complex may cleave, from an immobilized nucleic acid substrate, a small fragment bearing a detectable label. Then, detection of a free label in the reaction medium is indicative of the activity of the catalytic complex, which is in turn an indication of the presence of the assayed agent in the medium"). Asher et al. also disclose aptazyme constructs that bind to said tagged substrates in the presence of an analyte, but do not bind to said tagged substrates in the absence of said analyte (e.g., see figure 1, step 4(a) showing "Pro" i.e., a protein analyze; see also abstract, "The present invention concerns nucleic acid molecules [aptazymes] ... which have no catalytic activity in the absence of a specific co-factor [i.e., the "Pro"], and feature catalytic activity only in the presence of a specific co-factor"; see also Examples which employ multiple rounds of positive and negative screening steps to obtain this goal). Finally, Asher et al. also disclose contacting said aptazyme constructs and substrate within a sample suspected of containing said analyte under conditions which allow for substrate binding, washing away unbound substrate and detecting the bound substrate, thereby determining the presence of the analyte (e.g., see figure 1, steps 4-5, especially step 4 showing unbound substrate being "washed" off the solid support; see also claims 1, 9 and 15; see also page 31, "Negative Selection" step; see also method steps bridging pages 7-8 and also page 8, lines 16-28, "Other examples of catalytic activity which can be determined in step (c) are ligation ... In ligation ... two sequences are brought together ... One of these sequences may bear, for example, a fluorescent containing moiety (e.g. rhodaminc), and the other sequence may bear a fluorescent quenching (e.g. fluorescein) containing moiety or a fluorescent enhancing moiety; the

change in the distance between the two sequences may then be determined by measuring the change in fluorescence emission, which is quenched (in the case of a fluorescent quencher) or enhanced (in the case of a fluorescent enhancer) when the two sequences are adjacent one another, and enhanced or quenched, respectively, when the two sequences are spaced apart").

Response

13. Applicant's arguments directed to the above 35 U.S.C. § 102 rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "The Asher reference describes a method of *in vitro* selection to identify and generate aptazyme constructs. There is no teaching or suggestion to produce aptazyme arrays from aptazyme constructs already identified through an in vitro selection process for detecting an analyte and/or an aptazyme reaction, let alone automate such methods of detection" (e.g., see 10/27/04 Response, page 12, first full paragraph).

[2] Applicants argue, "... the aptazyme constructs used as a diagnostic tool in Asher are in suspension/solution, not immobilized to solid support or in array form, as in the instant invention" (e.g., see 10/27/04 Response, page 12, first full paragraph).

[3] Applicants argue, "Asher teaches that a solution of aptazyme constructs is added to immobilized nucleic acid substrates, whereas in the instant invention, analytes and tagged

nucleic acid substrates are added to immobilized, aptazyme constructs" (e.g., see 10/27/04 Response, page 12, first full paragraph).

[4] Applicants argue, "... the catalytic complex in Asher cleaves from the immobilized nucleic acid substrate a small detectable label, and the amount of free label is detected in the reaction medium, whereas in the instant invention, the analyte causes the tagged (labeled) nucleic acid substrate to covalently bind to the immobilized aptazyme, unbound substrate is washed away, and the immobilized labeled substrate is detected" (e.g., see 10/27/04 Response, page 12, first full paragraph).

[5] Applicants argue, "Furthermore, Applicant's specification distinguishes the instant invention from prior inventions by stating the advantage of having covalently immobilized aptazyme constructs for in vitro diagnostics (see page 15, 'covalent immobilization of reporters ... allows stringent wash steps to be employed')." (e.g., see 10/27/04 Response, page 12, first full paragraph).

This is not found persuasive for the following reasons:

[1] In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., **[1]** aptazyme constructs "already identified through an in vitro selection process" and **[2]** "automation") are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

[2] The Examiner respectfully disagrees (e.g., see figure 1 step 3 showing the immobilization processes using streptavidin/avidin as the linker; see also page 4, lines 18-22,

"The biotin, is then allowed to react with avidin which is present on a solid support, such as Stepravidin beads (SA), so that each molecule of the random array becomes immobilized onto a solid support").

[3] In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., analytes and tagged nucleic acid substrates are "added to" immobilized, aptazyme constructs) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Here, the claims only require that the aptazyme constructs be "immobilized" on the solid support and that the said aptazyme constructs be contacted with a substrate tagged with a detectable label. The order in which this is to occur is not specified in the claims. For example, due to the "comprising" language, the claim of course encompasses processes comprising these steps and any others. In addition, the recited steps need not even be carried out in the recited order. See Interactive *Gift Express, Inc. v. Compuserve Inc.*, 231 F.3d 859, 875, 56 USPQ2d 1647, 1661 (Fed. Cir. 2000) ("Unless the steps of a method actually recite an order, the steps are not ordinarily construed to require one.").

[4] The Examiner contends that many embodiments for detecting the analyte are disclosed by Asher et al. including, for example, "ligation" wherein the labeled substrate is bound immobilized and unbound substrate is washed away ((e.g., see figure 1, steps 4-5, especially step 4 showing unbound substrate being "washed" off the solid support; see also claims 1, 9 and 15; see also page 31, "Negative Selection" step; see also method steps bridging pages 7-8 and also page 8, lines 16-28, "Other examples of catalytic activity which can be

determined in step (c) are ligation ... In ligation ... two sequences are brought together ... One of these sequences may bear, for example, a fluorescent containing moiety (e.g. rhodaminc), and the other sequence may bear a fluorescent quenching (e.g. fluorescein) containing moiety or a fluorescent enhancing moiety; the change in the distance between the two sequences may then be determined by measuring the change in fluorescence emission, which is quenched (in the case of a fluorescent quencher) or enhanced (in the case of a fluorescent enhancer) when the two sequences are adjacent one another, and enhanced or quenched, respectively, when the two sequences are spaced apart"). The unbound "non-ligated" substrate is subsequently washed away and the enzyme activity can be detected by the bound substrate.

[5] In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (e.g., "in vitro diagnostics" and "stringent wash steps") are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Accordingly, the 35 U.S.C. 102 rejection cited above is hereby maintained.

Claims Rejections – 35 U.S.C. 102/103

14. Claims 47-49 and 54-57, 59-64 and 66 are rejected under 35 U.S.C. 102(a) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Marshall et al (Marshall, K. A.; Ellington, A. D. "Training ribozymes to switch" Nature Structural Biology **November 1999**, 6 (11), 992-4).

For ***claims 47, 59 and 66***, Marshall et al discloses "aptazyme chips" wherein different ribozyme ligases are immobilized on beads in wells to monitor the presence and concentrations of different metabolites or proteins (see Marshall et al, entire document, especially figure 3; see also page 994, last paragraph), which anticipates claims 47, 59 and 66. For example, Marshall et al discloses aptazyme chips for "monitor[ing] the presence and concentrations of different metabolites or proteins" wherein a "ribozyme ligase", which anticipates the preamble of claim 47 because an "aptazyme reaction" is being "detected" when the ribozyme ligase covalently bonds to a reporter in the presence of cognate effectors. Marshall et al also discloses "aptazymes" on a solid support i.e., they are disclosing "apatazyme chips", which reads on lines 2-5 of claim 47 (see Marshall et al, figure 3, "ribozyme ligases ... are shown immobilized on beads in wells ... [o]ne advantage of this scheme is that covalent immobilization of reporters ... should allow extremely stringent wash steps to be employed"). Marshall et al also discloses "at least one analyte" and "providing substrate tagged to be detectable" in lines 7-8 of claim 47 (see Marshall et al, figure 3, "ribozyme ligases ... immobilized on beads in wells and mixtures of analytes and fluorescently tagged substrates have been added to each well"). Marshall et al also discloses the immobilization of a substrate to the aptazyme upon activation of the aptazyme with an analyte wherein a signal is produced after washing unbound substrate off the substrate (see Marshall et al, figure 3, "after reaction and washing, the presence and amounts of co-immobilized fluorescent tags are indicative of he amounts of ligands that were present during the reaction").

For **claims 48 and 60**, although Marshall et al does not specifically mention the use of "automation" with disclosed methods for using "aptazyme chips", automation would be would be immediately envisaged (e.g., anticipated) or in the alternative prima facie obvious to one of ordinary skill in the art because "chip" are made for automation i.e., they are used and designed for high throughput screening. See *In re Schaumann*, 572 F.2d 312. 197 USPQ 5 (CCPA 1978).

For **claims 49 and 61**, Marshall et al discloses the use of "amplification" for increasing the amount of aptamer or aptazyme with the desired characteristics and thus increase the signal produced (see Marshall et al, figure 1) (see also Marshall, page 994 last paragraph, "Interestingly, aptazyme ligases have the unique property of being able to transduce effectors into templates that can be amplified, affording an additional boost in signal prior to detection"), which anticipates claim 49.

For ***claims 54 and 62***, Marshall et al discloses fluorescently tagged substrates (see Marshall et al, page 993, figure 3).

For ***claims 55-56 and 63-64***, Marshall et al discloses beads in wells on a multiwell plate (see Marshall et al, page 993, figure 3).

For ***claim 57***, Marshall et al discloses different aptazymes immobilized in different wells (see Marshall et al, page 993, figure 3).

15. Claims 47-49, 56, 59-62 and 66 are rejected under 35 U.S.C. 102(a) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Hesselberth et al (Hesselberth,

J.; Robertson, M. P.; Jhaveri, S.; Ellington, A. D. "In vitro selection of nucleic acids for diagnostic applications" Reviews in Molecular Biotechnology March 2000, 74, 15-25).

For ***claims 47, 59 and 66***, Hesselberth et al discloses methods for the "high-throughput construction of chips to sense proteomes and metabolomes" (see Hesselberth et al, entire document, pages 23-24; section 5), which anticipates claim 47. For example, Hesselberth et al discloses that "aptazymes" can be "covalently immobilize[d] ... in discrete sectors of arrays" like "chip[s]" (see Hesselberth et al, page 24, last paragraph, "For example, a host of signaling aptamers could be synthesized with terminal amines, immobilized on glass, and an analyte mixture could be applied to the glass surface"). Hesselberth et al also discloses method steps for using the immobilized aptazymes to detect individual analytes by their ability to "pull down" labeled substrates that can then be detected after washing away unbound substrate (see Hesselberth et al, page 24, last paragraph, "The presence of quantities of individual analytes could then be determined by monitoring the changes in fluorescence intensity in individual sectors of the chip. Similarly, aptazymes could be immobilized and analytes and oligonucleotide tags introduced together. Since the pairing between the aptazymes and the oligonucleotide tags can be altered at will, analytes could activate specific aptamers in specific sectors to pull down specific tags. In this way, analyte detection might not only be spatially but also spectrally resolved. Moreover because the tags are covalently immobilized to the aptazyme, which in turn covalently immobilized to the chip surface, aptazyme chips can be stringently washed to reduce non-specific binding and background").

For ***claims 48 and 60***, although Hesselberth et al does not specifically mention the use of "automation" with disclosed methods for using the "chips", automation would be would be immediately envisaged (e.g., anticipated) or in the alternative prima facie obvious to one of ordinary skill in the art because "chip" are made for automation i.e., they are used and designed for high throughput screening. See *In re Schaumann*, 572 F.2d 312. 197 USPQ 5 (CCPA 1978).

For ***claims 49 and 61***, Hesselberth et al discloses the ribozymes with appended tags can be "preferentially amplified" (see Hesselberth et al, entire document, especially page 16, paragraph 1), which anticipates claim 49.

For ***claims 54 and 62***, Hesselberth et al discloses fluorescent substrates (see Hesselberth et al, page 24, column 1, last paragraph).

Response

16. Applicant's arguments directed to the above 35 U.S.C. § 102/103 rejection(s) were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicants argue, "As described above and in the new Affidavit submitted herewith, the Marshall reference is not available as prior art under 35 U.S.C. § 102 or under 35 U.S.C. § 103" (e.g., see 10/27/04 Response, pages 7-8; see also Hesselberth section where similar arguments were made).

This is not found persuasive for the following reasons:

The Examiner contends that the Declaration/Affidavit is defective because **[1]** although it is not clear whether Applicants are trying to antedate the reference under 37 C.F. R. § 1.131 or show attribution under 37 C.F.R. § 1.132, to the extent that Applicants are trying to antedate the reference the Examiner contends that no evidentiary support for this position has been provided. With respect to filing declarations under 37 CFR § 1.131, the showing of facts shall be such, in character and weight, as to establish reduction to practice prior or the effective date of the reference, or conception of the invention prior to the effective date of the reference coupled with due diligence from said date to a subsequent reduction to practice or to the filing of the application. Original exhibits or drawings or records or photocopies thereof ***must accompany and form part of the affidavit or declaration*** or their absence satisfactorily explained. See MPEP §715.07. Furthermore, the Declaration/Affidavit is defective because **[2]** it does not include the name of one of the inventors i.e., Kristin Thompson (e.g., see 2/11/04 Declaration of Prior Invention under 37 C.F. R. § 1.131, "We, Andrew Ellington, Kristin Thompson and Michael Robertson, invented the inventions claimed in the case" (emphasis added); see also signature dated 2/9/04 by Kristin Thompson on page 6) and thus cannot be used to antedate the reference because there is no statement explaining that less than all of the inventors contributed to the claimed invention (e.g., see MPEP § 715.04). Finally, to the extent that Applicants are trying to show attribution (e.g., Katz declaration) the new supplemental Declaration/Affidavit is also defective because **[3]** there is evidence that it does not represent Applicants' own work (e.g., see MPEP § 716.10, "An uncontradicted 'unequivocal statement' from the applicant regarding the subject matter disclosed in an article, patent, or published application will be accepted as establishing inventorship. In re DeBaun, 687 F.2d 459, 463, 214 USPQ 933, 936 (CCPA 1982).

However, a statement by the applicants regarding their inventorship in view of an article, patent, or published application ***may not be sufficient where there is evidence to the contrary***. Ex parte Kroger, 218 USPQ 370 (Bd. App. 1982) (a rejection under 35 U.S.C. 102(f) was affirmed notwithstanding declarations by the alleged actual inventors as to their inventorship in view of a nonapplicant author submitting a letter declaring the author's inventorship); In re Carreira, 532 F.2d 1356, 189 USPQ 461 (CCPA 1976) (disclaiming declarations from patentees were directed at the generic invention and not at the claimed species, hence no need to consider derivation of the subject matter)"). In the present case, as in Ex parte Kroger, a nonapplicant [Kristin Thompson, formerly Kristin Marshall] has submitted a letter declaring the author's inventorship (e.g., see 2/11/04 Declaration of Prior Invention under 37 C.F. R. § 1.131, "We, Andrew Ellington, Kristin Thompson [formerly Kristin Marshall] and Michael Robertson, invented the inventions claimed in the case" (emphasis added); see also signature dated 2/9/04 by Kristin Thompson on page 6). Thus, sufficient evidence has been set forth consistent with *Ex parte Krogre*. Furthermore, if Applicants intend a declaration of attribution then Applicants should file said declaration under 37 C.F.R. § 1.132 to make their intentions clear.

Accordingly, the 35 U.S.C. 102/103 rejection(s) cited above are hereby maintained.

Claim Rejections - 35 USC § 103

17. Claims 47-49, 54-57, 59-64 and 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marshall et al (Marshall, K. A.; Ellington, A. D. "Training ribozymes to switch" Nature Structural Biology **November 1999**, 6 (11), 992-4) and Cox et al (Cox, J. C.; Rudolph, P.; Ellington, A. D. "Automated RNA Selection" *Biotechnol. Prog.* **1998**, 14, 845-850).

For **claims 47, 49, 54-57, 59, 61-64 and 66**, Marshall et al teaches all the limitations stated in the 35 U.S.C. 102(a) rejection above (incorporated in its entirety herein by reference), which anticipates claims 47, 49, 54-59, 61-66 and, consequently, also renders obvious claims 47, 49, 54-59, 61-66.

For ***claims 48 and 60***, the prior art teachings of Marshall et al differs from the claimed invention by not specifically reciting the use of a "automation" for the method of detecting an aptazyme reaction. Marshall et al is deficient in that it only teaches the use of "chips", which only implies that automation would be used since chips are designed for large scale automation (see Marshall et al, page 993, figure 3).

However, Cox teaches that in vitro selection can be "automated" (see entire document, especially figure 1).

Thus, it would have been obvious to one skilled in the art at the time the invention was made to use the method of Marshall et al with the "automation" equipment as taught by Cox et al because Cox et al teaches that their automation procedures can be used with aptamers in procedures that involve in vitro selection as required by the method steps Marshall et al. Furthermore, one of ordinary skill in the art would have been motivated to use a "automation" because Cox explicitly states that "[a]utomated selection can now be used to generate nucleic acid aptamers in days rather than weeks or months" i.e. one of skill in the art would have immediately recognized the time savings that could be obtained through automation and the possibility of increased throughput (see Cox et al, entire document, especially abstract).

18. Claims 47, 49, 54, 61-62 and 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hesselberth et al (Hesselberth, J.; Robertson, M. P.; Jhaveri, S.; Ellington, A. D. "In vitro selection of nucleic acids for diagnostic applications" Reviews in Molecular Biotechnology March 2000, 74, 15-25) and Cox et al (Cox, J. C.; Rudolph, P.; Ellington, A. D. "Automated RNA Selection" Biotechnol. Prog. **1998**, 14, 845-850).

For **claims 47, 49, 54, 61-62 and 66**, Hesselberth et al teaches all the limitations stated in the 35 U.S.C. 102(a) rejection above (incorporated in its entirety herein by reference), which anticipates claims 47, 49, 54, 58, 61-62, 65-66 and, consequently, also renders obvious claims 47, 49, 54, 61-62, 65-66.

For ***claims 48 and 60***, the prior art teachings of Hesselberth et al differs from the claimed invention by not specifically reciting the use of a "automation" for the method of detecting an aptazyme reaction. Hesselberth et al is deficient in that it only teaches the use of "chips", which only implies that automation would be used since chips are designed for large scale automation (see Hesselberth et al, page 24, last paragraph; see also abstract).

However, Cox teaches that in vitro selection can be "automated" (see entire document, especially figure 1).

Thus, it would have been obvious to one skilled in the art at the time the invention was made to use the method of Hesselberth et al with the "automation" equipment as taught by Cox et al because Cox et al teaches that their automation procedures can be used with aptamers in procedures that involve *in vitro* selection as required by the method

steps Hesselberth et al. Furthermore, one of ordinary skill in the art would have been motivated to use a "automation" because Cox explicitly states that "[a]utomated selection can now be used to generate nucleic acid aptamers in days rather than weeks or months" i.e. one of skill in the art would have immediately recognized the time savings that could be obtained through automation and the possibility of increased throughput (see Cox et al, entire document, especially abstract).

Response

19. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection(s) were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicants argue, "As described above and in the new Affidavit submitted herewith, the Marshall reference is not available as prior art under 35 U.S.C. § 102 or under 35 U.S.C. § 103" (e.g., see 10/27/04 Response, pages 8-10; see also Hesselberth and Cox section where similar arguments were made).

This is not found persuasive for the following reasons:

The Examiner contends that the Declaration/Affidavit is defective because **[1]** although it is not clear whether Applicants are trying to antedate the reference under 37 C.F. R. § 1.131 or show attribution under 37 C.F.R. § 1.132, to the extent that Applicants are trying to antedate the reference the Examiner contends that no evidentiary support for this position has been provided. With respect to filing declarations under 37 CFR § 1.131, the showing of facts shall be such, in

character and weight, as to establish reduction to practice prior or the effective date of the reference, or conception of the invention prior to the effective date of the reference coupled with due diligence from said date to a subsequent reduction to practice or to the filing of the application. Original exhibits or drawings or records or photocopies thereof ***must accompany and form part of the affidavit or declaration*** or their absence satisfactorily explained. See MPEP §715.07. Furthermore, the Declaration/Affidavit is defective because **[2]** it does not include the name of one of the inventors i.e., Kristin Thompson (e.g., see 2/11/04 Declaration of Prior Invention under 37 C.F. R. § 1.131, "We, Andrew Ellington, Kristin Thompson and Michael Robertson, invented the inventions claimed in the case" (emphasis added); see also signature dated 2/9/04 by Kristin Thompson on page 6) and thus cannot be used to antedate the reference because there is no statement explaining that less than all of the inventors contributed to the claimed invention (e.g., see MPEP § 715.04). Finally, to the extent that Applicants are trying to show attribution (e.g., Katz declaration) the new supplemental Declaration/Affidavit is also defective because **[3]** there is evidence that it does not represent Applicants' own work (e.g., see MPEP § 716.10, "An uncontradicted 'unequivocal statement' from the applicant regarding the subject matter disclosed in an article, patent, or published application will be accepted as establishing inventorship. In re DeBaun, 687 F.2d 459, 463, 214 USPQ 933, 936 (CCPA 1982). However, a statement by the applicants regarding their inventorship in view of an article, patent, or published application ***may not be sufficient where there is evidence to the contrary***. Ex parte Kroger, 218 USPQ 370 (Bd. App. 1982) (a rejection under 35 U.S.C. 102(f) was affirmed notwithstanding declarations by the alleged actual inventors as to their inventorship in view of a nonapplicant author submitting a letter declaring the author's inventorship); In re Carreira, 532

F.2d 1356, 189 USPQ 461 (CCPA 1976) (disclaiming declarations from patentees were directed at the generic invention and not at the claimed species, hence no need to consider derivation of the subject matter)"). In the present case, as in Ex parte Kroger, a nonapplicant [Kristin Thompson, formerly Kristin Marshall] has submitted a letter declaring the author's inventorship (e.g., see 2/11/04 Declaration of Prior Invention under 37 C.F. R. § 1.131, "We, Andrew Ellington, Kristin Thompson [formerly Kristin Marshall] and Michael Robertson, invented the inventions claimed in the case" (emphasis added); see also signature dated 2/9/04 by Kristin Thompson on page 6). Thus, sufficient evidence has been set forth consistent with *Ex parte Krogre*. Furthermore, if Applicants intend a declaration of attribution then Applicants should file said declaration under 37 C.F.R. § 1.132 to make their intentions clear.

Accordingly, the 35 U.S.C. 103(a) rejection cited above is hereby maintained.

20. Claims 47-49, 54-57, 59-64 and 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Asher et al (WO 98/08974) (Date of Publication is **March 5, 1998**) and Breaker (WO 98/27104) (Date of Publication is **June 25, 1998**).

For ***claims 47, 59 and 66***, Asher et al. disclose (see entire document) catalytic nucleic acids and their diagnostic use (see Asher et al, abstract), which reads on claims 47, 59 and 66. For example, Asher et al. disclose providing an array having one or more aptazyme constructs disposed thereon at discrete locations by immobilization of said aptazyme constructs on a solid support (e.g., see figure 1 step 3 showing the immobilization processes using streptavidin/avidin as the linker; see also page 4, lines

18-22, "The biotin, is then allowed to react with avidin which is present on a solid support, such as Streptavidin beads (SA), so that each molecule of the random array becomes immobilized onto a solid support"). Please note that the aptazyme constructs in this scenario comprise a random sequence (R) that cleave the substrate (S) in "cis" (e.g., see page 24, Example 1, lines 9-15; see also figure 1, step 1, see also figure 1, step 4(b)(i) and 4(b)(ii); see also page 14, lines 21-29). In addition, Asher et al. disclose contacting said aptazyme constructs with a substrate tagged with a detectable label (e.g., see figure 1, step 1 wherein the substrate is represented by the "S" i.e., the aptazyme is cis-acting; see also figure 1, step 6 wherein a PCR amplified tag is shown; see also page 16, last paragraph; see also page 8, lines 10-15, "For example, the catalytic complex may cleave, from an immobilized nucleic acid substrate, a small fragment bearing a detectable label. Then, detection of a free label in the reaction medium is indicative of the activity of the catalytic complex, which is in turn an indication of the presence of the assayed agent in the medium"). Asher et al. also disclose aptazyme constructs that bind to said tagged substrates in the presence of an analyte, but do not bind to said tagged substrates in the absence of said analyte (e.g., see figure 1, step 4(a) showing "Pro" i.e., a protein analyze; see also abstract, "The present invention concerns nucleic acid molecules [aptazymes] ... which have no catalytic activity in the absence of a specific co-factor [i.e., the "Pro"], and feature catalytic activity only in the presence of a specific co-factor"; see also Examples which employ multiple rounds of positive and negative screening steps to obtain this goal). Finally, Asher et al. also disclose contacting said aptazyme constructs and substrate within a sample suspected of containing said analyte under conditions which

allow for substrate binding, washing away unbound substrate and detecting the bound substrate, thereby determining the presence of the analyte (e.g., see figure 1, steps 4-5, especially step 4 showing unbound substrate being "washed" off the solid support; see also claims 1, 9 and 15; see also page 31, "Negative Selection" step).

For ***claims 49 and 61***, Asher et al disclose amplifying the signal by various means including self amplifying ribozyme cascade reactions and PCR (e.g., see page 9, line 8 wherein a self amplifying ribozyme cascade reaction is reporter; see also page 16, last paragraph).

For ***claims 54 and 62***, Asher et al disclose fluorescently labeled RNA constructs (e.g., see figure 19).

For ***claims 55 and 63***, Asher et al disclose Streptavidin beads (e.g., see page 24, lines 20-21).

The prior art teachings of Asher et al differ from the claimed invention as follows:

For ***claim 47***, Asher et al are deficient in that they do not specifically recite the use of "covalent" immobilization. Asher et al. only disclose the use of streptavidin/avidin as an example (e.g., see figure 1).

For ***claim 48***, Asher et al are deficient in that they do not disclose automation.

For ***claim 56 and 57***, Asher et al are deficient in that they do not disclose a bead in the well of a multiwell plate.

However, Breaker teaches the following limitations that are deficient in Asher et al:

For ***claim 47***, Breaker (see entire document) teaches the use of covalent bonding of the aptazymes to the solid support (e.g., see page 18, lines 6-11, "A variety of different chromatographic resins and coupling methods can be employed to immobilize DNA enzymes. For example, a simple non-covalent method that takes advantage of the strong binding affinity of streptavidin for biotin to carryout a model experiment is illustrated in Figure 3. In other embodiments, DNA enzymes can be coupled to the column supports via covalent links to the matrix, thereby creating a longer-lived catalytic support").

For ***claims 48 and 60***, Breaker discloses automation (e.g., see page 17, line 21).

For ***claims 56 and 57***, Breaker teaches biosensors on a solid-support which are commonly performed on multiwell plates (e.g., see pages 1-2). Furthermore, the beads in the wells would have to contain different constructs in order for the "biosensor" to work e.g., if they had the same construct immobilized in every well it wouldn't function as a biosensor.

It would have been obvious to one skilled in the art at the time the invention was made to make the immobilized array of aptazymes as taught by Asher et al with covalent attachment of the aptazymes to the solid-support as taught by Breaker instead of by Streptavidin/Avid immobilization as taught by Asher et al because Breaker explicitly states that aptazymes can be immobilized in this fashion and for this purpose (e.g., see page 18, lines 6-11, "A variety of different chromatographic resins and coupling methods can be employed to immobilize DNA enzymes. For example, a simple non-covalent method that takes advantage of the strong binding affinity of streptavidin for biotin to carryout a model experiment is illustrated in Figure 3. In other embodiments, DNA

enzymes can be coupled to the column supports via covalent links to the matrix, thereby creating a longer-lived catalytic support"). A person would have been motivated to use the covalent links taught by Breaker et al because the reference explicitly states that they provide for "longer-lived catalytic support" i.e., they are more stable than the streptavidin/avidin complexes. Finally, one of ordinary skill in the art would have reasonably expected to be successful because Breaker teaches a "wide variety" of coupling methods exist for immobilizing aptazymes including streptavidin/avidin and covalent modification and that all of the methods can be used successfully i.e., these procedures are well known in the art to be successful (see Breaker,).

Furthermore, a person of skill in the art would have also been motivated to use the allosterically controlled "DNA" Enzymes disclosed by Breaker in place of the "RNA" Enzymes disclosed by Asher et al. because Breaker explicitly states that "DNA" enzymes are better than "RNA" enzymes because of their increased stability (e.g., see page 18, paragraph 1, "The function of catalytic DNAs to create enzyme coated surfaces that can be used in various catalytic processes is described herein and illustrated in Figure 4. Due to the high stability of the DNA phosphodiester bond, such surfaces are expected to remain active for much longer than similar surfaces that are be coated with protein- or RNA-based enzymes"). Furthermore, a person of skill in the art would have reasonably expected to be successful because both references state that these nucleic acids (both RNA/DNA) can be used for biological assays.

Response

21. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "As discussed above, Asher is distinguishable from the instant invention ..." (e.g., see 10/27/04 Response, pages 12-13, especially page 13, last paragraph).

[2] Applicants argue, "The use of automation in Breaker II refers to an automated in vitro selection method for selecting DNA molecules, not an automated method for detecting aptazyme reactions using aptazyme arrays" (e.g., see 10/27/04 Response, page 13, last paragraph).

[3] Applicants argue, "... Breaker II is insufficient to render the claimed invention obvious because there is no teach or suggestion in this reference that would motivate one of ordinary skill in the art to produce an automated method for detecting aptazyme reactions using aptazyme chips" (e.g., see 10/27/04 Response, page 13, last paragraph).

This is not found persuasive for the following reasons:

[1] The Examiner contends that to the extent that Applicants are applying the same arguments to the above Asher et al. 35 U.S.C. § 102 rejection, those issues were adequately addressed in that section, which is incorporated in its entirety herein by reference.

[2] In response to applicant's arguments against the Breaker II reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

[3] In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, a person of skill in the art would have bee motivated to combine the teachings of Asher et al. and Breaker to arrive at Applicants' claimed invention because Breaker et al explicitly states that they provide for "longer-lived catalytic support" i.e., they are more stable than the streptavidin/avidin complexes. Furthermore, a person of skill in the art would have also been motivated to use the allosterically controlled "DNA" Enzymes disclosed by Breaker in place of the "RNA" Enzymes disclosed by Asher et al. because Breaker explicitly states that "DNA" enzymes are better than "RNA" enzymes because of their increased stability (e.g., see page 18, paragraph 1, "The function of catalytic DNAs to create enzyme coated surfaces that can be used in various catalytic processes is described herein and illustrated in Figure 4. Due to the high stability of the DNA phosphodiester bond, such surfaces are expected to remain active for much longer than similar surfaces that are be coated with protein- or RNA-based enzymes").

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

Conclusion

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
January 1, 2004

BENNETT CELSA
PRIMARY EXAMINER